



**NTP**  
National Toxicology Program

# Concept Review for Valerian

Michael DeVito, PhD  
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors  
December 9-10, 2009





## Valerian

- Most commonly refers to extracts of the underground rhizomes and roots from the species *V.officinalis*
  - Includes tinctures, essential oils, terpenes, terpene-free fractions, and residues
- Used for neurological and/or psychological ailments
  - Insomnia, mood disorders, anxiety, and psychological stress conditions.
  - Also used in treatment of menstrual cramps and menopausal symptoms (insomnia)



## **NTP Nomination**

- Nominated by the NIEHS
- 11<sup>th</sup> top selling botanical dietary substance (Herbal Gram, 2009)
- A number of products contain valerian as the main constituent or in combination with other herbs.
- Limited toxicological data



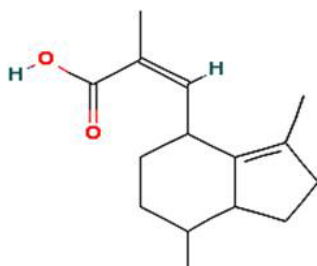
## Constituents

- 150 Different Constituents
  - Sesquiterpenoids, including bornyl acetate, isovalerate and valerenic acid, make up approximately 10-40% of the essential oil.
  - Valepotriates are epoxy iridoid esters that are found up to 2% of the dried root.
    - Valepotriates are not readily absorbed because they are rapidly degraded in acid to baldrinal and homobaldrinal

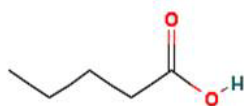
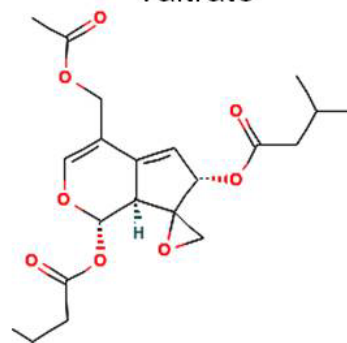


## Chemical Structures

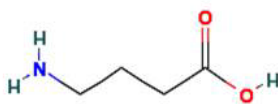
Valerenic acid



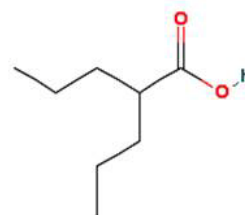
Valtrate



Valeric acid



GABA



Valproic acid



## Human Exposure and Clinical Data

- Exposure
  - 5.6% took valerian w/in last 12 months (Kennedy, 2005)
  - 9.5% of students at small southeastern private college took valerian (Stasio et al 2008)
- Clinical Data
  - Some evidence that valerian has sedative activity
    - Bent et al 2006 – Meta analysis of 16 clinical trials involving 1093 patients suggests valerian improves sleep quality with minimal side effects.
    - Taibi et al 2007 – reviewed 37 clinical trials (1900 patients) suggests valerian does not impair or improve psychomotor or cognitive abilities or induce sedation.



## **Toxicological Data**

- Limited studies available
  - Most studies focused on pharmacological effects
  - Two developmental studies
    - Used either an ethanolic extract or a mixture of pure constituents
  - In vivo evidence of DNA damage in 90 day male mouse study
    - Examined markers of genotoxicity in reproductive and hematopoietic tissue (blood and femur)
  - No chronic toxicity studies available
- LD50
  - Extracts are in the 1.5 g/kg or higher
  - Individual constituents 60 mg/kg or higher



## Key Issues

- Human Exposure
  - Widely used supplement
- Limited Toxicological Evaluations
  - No chronic toxicity studies
  - Inadequate developmental studies





## Testing Challenges

- Which preparation to evaluate
  - Includes tinctures, essential oils, terpenes, terpene-free fractions, and residues
- Toxicological endpoints
  - Neurotoxicity (adult and developmental)
  - Toxicities not associated with the pharmacological effects.



## Consensus Preparation

- In collaboration with FDA, determine the *Valerian* species used in modern valerian preparations; establish a consensus valerian root preparation (sesquiterpene, valepotriates, etc. content).



## Screening Strategy

- Which preparation to evaluate
  - Tiered approach
    - Tier 1 **Chemical characterization**
      - Compare extraction procedures based on valerenic acid content
    - Tier 2 **In vitro screens**
      - Interactions with GABA receptors
      - Mutagenicity
    - Tier 3 **In vivo studies**
      - Acute studies on motor activity



## Testing Strategy

- Tiered Approach
  - Tier 1 Repeat Dose Study
    - Dose range finding study and identify target tissue
  - Tier 2 Reproductive and Developmental Studies
  - Tier 3 Chronic Studies



## **Significance of Proposed Research Program**

- Provides toxicological data necessary enabling:
  - (i) understanding of toxicity of valerian root and its constituents;
  - (ii) providing data for developing regulatory policy for valerian dietary supplements and herbal preparations.